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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,799	12/20/2001	Beuford Arlie Bogue	24720	4794

20551 7590 12/27/2006

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/27/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/022,799	BOGUE, BEUFORD ARLIE	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,21-28,30-36 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,21-28,30-36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment and response dated 9-30-06 is acknowledged.

Claims 18, 21-28, 30-36 and 38 are pending in the instant application.

Response to Arguments

Applicant's arguments filed 9-30-06 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

1. Claim 18, 21-28, 30-36 and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of improving the solubility of dimenhydrinate by processing dimenhydrinate into Pluronic surfactant, does not reasonably provide enablement for improving the solubility of or all the drugs with any surfactant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Instant claims are directed to a method of improving solubility of a drug by processing the drug into a surfactant-coated particulate form comprising the steps of

1. Melting the drug into a molten surfactant miscible with the drug,

2. Heating the mixtures to above the melting temperature and below the drug's decomposition temperature until a clear mixture is formed,

3. Cooling the mixture to approximately room temperature while continuously mixing under high shear to maximize the precipitation of the particles.

Instant claims broadly recite, "improving drug solubility" and 'surfactant", thus encompassing innumerable drugs and surfactants. The claimed "drugs" according to the specification (as well as claim 22) include several classes of drug. It is generally known in the art that drug dissolution depends on the nature of the drugs i.e., water soluble and insoluble drugs have different dissolution patterns upon administration. Instant specification describes that to increase the solubility the drug is first added to a molten surfactant, melting the mixture and cooling under high shear. Instant specification describes the method of improving the solubility of the drug dimenhydrinate with a surfactant Pluronic. The process of improving the solubility described in the specification only employs grinding the drug-surfactant melt in a mortar and pestle (high shear) so as to form the claimed coated particles. However, instant specification does not provide any guidance if this method of melting and grinding in a mortar and pestle results in a surfactant coated microparticles for all the drugs and with a all the surfactants. This is further supported by applicants' description that in order to obtain sufficient cooling, such that the crystals do not grow on the surfactant, cooling should be performed under high shear (0064-0065). In the absence of what constitutes a high shear –is it simple grinding or a high vortexing or centrifuging at high speeds such as 3000 rpm etc., one cannot extrapolate the method practiced with one drug (in the specification) to all possible drugs and surfactants because not all the drugs and surfactants have the same melting points, and therefore the mixtures have different eutectic temperatures and also the cooling rates vary with drugs and surfactants employed. The specification admits that for stability reasons, the surfactant should have a melting point above room

temperature and preferably, above 40 degrees C (0061). Thus, the final outcome of the claimed method i.e., drug with improved solubility depends several factors such as on the type or solubility of the drug, melting point of the surfactant, the high shear employed (such that the cooling occurs properly), all of which are specific depending on the drug and surfactant and the eutectic mixture. In the absence of the guidance as to how to optimize the above conditions such that the solubility of any kind of drug can be improved and with the exemplification just one type of drug and one type of surfactant, one of an ordinary skill in the art at the time of the instant invention was made would not be able to practice the claimed method of improving the drug solubility with any drug, any surfactant.

RESPONSE: Applicants argue that the specification clearly sets forth types and solubilities for the drugs encompassed by the instant claims. It is stated that in addition to the classes of drugs listed on page 14, lines 5-11, the disclosure that the drugs "can be poorly soluble- that the drug substance has a solubility in a liquid dispersion medium of less than about 100 mg/ml, preferably less than about 1 mg/ml" provides ample guidance with respect to the suitable drugs. Applicants' arguments are not persuasive instant claims are not limited to any specific drug solubility nor the specification provides any definition of the drugs. The above description is only inclusive of the sparingly soluble drugs and not restricted to sparingly or insoluble drugs. Applicants themselves admit that in addition the drugs include other classes of drugs (page 14), which are described only by their function and not by their chemical structure. Thus, one of an ordinary skill in the art would have to first undertake painful selection of the types of

drugs that can be suitably mixed with a surfactant so as to prepare the claimed composition. Next, applicants argue that the suitable surfactants are described on pages 16-17. In addition, applicants state that the instant surfactants 'do not chemically react with the drug substance or itself" and that the molecules of the surfactant are essentially free of intermolecular cross-linkages. Applicant's arguments are not persuasive because the general description pertaining to the non-reactivity of the surfactant with the drug or the surfactants being free of intermolecular cross-linkages does not provide any guidance to a skilled artisan who wish to practice the instant invention with respect to what surfactants or types or classes of surfactants do not react with drug (all or specific types?) and if choosing a surfactant that does not react with a drug also lacks the required intermolecular cross-linkages. One of an ordinary skill in the art would not be able to easily choose a suitable surfactant for a particular drug because surfactants are further classified into anionic, nonionic, amphiphilic etc., and the description of surfactant provided I the instant specification does not enable one to choose a surfactant at least based on the above classification. While applicants argue that another requirement of the surfactant is that it should have a "melting point above room temperature and preferably above 40 degrees C", none of the claimed surfactants require the above feature nor instant specification describes what surfactants possess this property together with the above features. Furthermore, instant specification describes that the drug and surfactant are liquefied at a temperature below the decomposition temperature of the drug and typically done at eutectic temperature, which is lower than the drug decomposition temperature. Thus, even if the physical

properties such as melting point, decomposition temperature etc., of a given are known to one of an ordinary skill in the art, the criticality of the invention is that the melting process or liquefying the mixture is done at eutectic temperature, which in turn is dependent upon the surfactant used. Thus, the predictability of the final desired product is a function of the proper surfactant employed with a particular drug under consideration because the same surfactant may or may not have the same eutectic temperature with all the drugs. One of an ordinary skill in the art would have perform undue experimentation in choosing the appropriate surfactant, determine the eutectic temperature of the mixture such that a clear mixture is formed and then employ appropriate shear force to render the desired surfactant coated drug particle.

With respect to the shear forces, applicants argue that it is a common term of the art and would be readily understood by one of an ordinary skill in the art. Applicants admit that the instant specification does not define "shear force" and that there are a large variety of these devices readily ascertainable for the intended purpose. Further, applicants argue that vigorous mixing in a mortar and pestle (example 1 of the instant application) constitutes an example of high shear. However, the above argument is not persuasive because, the availability of a wide variety of shear forces does not necessarily enable one of an ordinary skill in the art to use any such force to practice the claimed invention. This is because admittedly wet grinding or shear methods (applicants' reference to the teachings of US 4,540,602 & US 5,858,410 in the instant description of related art), which according to the explanation should involve high shear forces, are not satisfactory in preparing the composition because of the resulting larger

particles. Instant specification fails to describe what constitutes an optimum "high shear force" (at least a range, such that the requirement that the drug crystals do not grow on the outside of the surfactant. Thus, without the guidance from the instant application as to what force constitutes high shear force and together with the absence of guidance with respect to the suitable drugs and surfactants, eutectic temperatures etc., other than the description of the method of improving the solubility of dimenhydrate hydrochloride and Pluronic NF F68, one of an ordinary skill in the art would have to practice the instant invention of improving the solubility of a desired drug with repeated trial and error in first selecting a suitable drug, determine the melting point and decomposition temperature of the drug, next select a surfactant that is miscible with the drug and finally optimizing the shear forces.

Claim Rejections - 35 USC § 103

3. Claims 18, 21-28, 30-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/40943 (WO).

WO teaches solubilizing delivery systems for poorly soluble drugs and the process of solubilizing the drugs so as to enhance the solubility of the drugs. The process of WO comprises processing of particles of at least one active agent and at least one solubilizing agent (surfactant) at temperatures below the melting points of both drug and surfactant (eutectic temperature). The processing further involves applying shear forces after melting the drug and surfactant at the eutectic temperatures (page 2,

lines 20-31; page 3, lines 6-16 and lines 26-30 & page 4, lines 1-3), resulting in crystalline drug particles coated with the surfactant. Thus, the process of WO reads on the instant claimed method steps. With respect to the melting points, instant claims require melting a mixture of drug and surfactant at a temperature above the melting point of the mixture, such that a clear mixture is formed. A review of the specification on pages 20 (lines 1-5) and 22-23 reveals that while a clear mixture results in micro and nano-crystals claimed, it is also stated that sometimes the inventive method also results in the formation of solid. Thus, it is not necessary that the claimed method always render a clear mixture. Further, instant figure 1 shows that the eutectic point of the drug and surfactant shows a melting point below the individual melting points of drug and surfactant. In this regard, WO also teaches processing drug and surfactant below their individual melting points. Even though instant claims recite "above the mixture's melting point", the said melting point of the mixture is still below their individual melting points of the drug and surfactant and thus meets the instant requirement. Accordingly, absent any unexpected results with the claimed " melting the mixture above the mixture's melting point", it would have been obviuous for one of an ordinary skill in the art at the time of the instant invention to use the melting temperatures suggested by WO and still prepare micro or nano-crystalline particulate drug substances.

WO teaches the claimed drugs and surfactants suitable for the invention on page 5 and 6; and their amounts on page 4, lines 17-25, all of which are claimed in the instant application. WO teaches employing micronized drug (example I) for the processing and hence meet claim 21. With respect to the particle size, WO states that the particle size

before processing is less than 10 microns or even preferably less than 6 microns (page 5, lines 16-18) and absent showing evidence to the contrary, the process of applying high shear (of WO), yields crystalline particles of much smaller size. The claimed matrix, miscibility and the absence of bonding between the drug and the surfactant is inherent to the composition of WO because the drug and surfactant are processed inexactly the same way as described in the instant specification. WO fails to specifically teach the carrier, diluent, binder etc., for the drug. However, WO suggests mixing the surfactant coated drug particles (after processing) with various pharmaceutical ingredients such as binders, flow control agents, fillers, sweeteners etc. Accordingly, it would have been within the scope of a skilled artisan at the time of the instant invention to include any suitable pharmaceutical additive such as a binder or sweetener depending the desired pharmaceutical effect.

RESPONSE: Applicants argue that WO fails to teach "applying shear forces after melting the drug and surfactant and heating the mixture until a clear solution is formed. They argue that even though the reference teaches the use of forces, there is no teaching of the use of the force on the melted clear solution, which is essential for the formation of micro- and nano-particulate crystals.

A thorough review of the instant disclosure reveals that the instant method of preparing the micro- and nano-particulate drug crystals wherein the eutectic drug-surfactant matrix is subject to high shear during a cooling step (page 13, L 20-24). Further, on page 19 (L 14-24) it is stated that drug will be melted below its decomposition temperature when added to molten surfactant in order to avoid the

decomposition temperature of the drug because a eutectic mixture generally has a melting temperature lower than the highest individual melting point of either component. Thus, instant method requires heating the drug and surfactant at eutectic temperature of the drug-surfactant. It is further shown from example 1, wherein the dimenhydrinate and pluronic were combined and heated to 90 degrees C until a clear liquid was obtained. It appears from the above example that the drug is simply mixed with the surfactant (pluronic) and heated to 90 C (eutectic temperature?).

WO recognizes that adding drug to a molten surfactant (Pluronic) to produce solid drug (ibuprofen) dispersions is known in the art (WO refers to the teachings of WO 97/02017 on page 1). Further, WO states that Pluronic mixed with ibuprofen results in an eutectic mixture (page 1, last paragraph). However, in order to improve the solubility of the drug, WO suggests employing a temperature below the melting of drug and solubilizer. Applicants argue that WO teaches processing at a temperature below the temperature at which the active dissolves in the solubilizer. However, the teaching of WO referred to is a preferred embodiment and the prior art teachings should be taken in to consideration as a whole and not limited to preferred embodiments. Accordingly, from the teaching of processing below the melting points of drug and solubilizer together with the teaching of a temperature range (from below the eutectic temperature of the active and solubilizer combination to below the temperature at which the active dissolves in the solubilizer), it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to choose the appropriate processing temperature upon mixing the active agent and solubilizer such that the desired solubility of the drug is

achieved. In this regard, WO also desires the same end product i.e., particles of drug coated with surfactant. Thus, the upper limit of the temperature (of WO) is still below the temperature at which the drug decomposition occurs. With respect to the shear forces, WO teaches that certain actives, especially drugs will form a eutectic material with certain solubilizers when processed under sufficient forces, which then result in the coating of the active agent.

Applicants' arguments that WO teaches away from the present invention to form of clear mixture has been considered but not found persuasive because WO teaches using appropriate combination of temperature and force, to form the eutectic and coat the particles of active with the solubilizer. Further, as explained above, WO suggests maintaining low temperature such that optimum sized crystals are formed, which renders the desired drug dissolution and accordingly, absent showing any unexpected advantage, optimizing the conditions of temperature and force for processing the drug and solubilizer, so as to obtain the coated active /drug particles would have been within the scope of a skilled artisan. WO clearly suggests the importance of the melting temperature and cooling step, in obtaining the desired crystals, which is also a function of active agent. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -6.30 PM

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Art Unit 1615
December 21, 2006

LAKSHMI S. CHANNAVAJJALA
PRIMARY EXAMINER